

Nonprescription Drugs Advisory Committee Meeting for Nicotine Mouth Spray 1 mg

FDA Introductory Remarks

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September 18, 2019

Meeting Objectives

- Discuss efficacy and safety of over-the-counter (OTC) nicotine mouth spray (NMS) for smoking cessation
- Discuss potential for abuse and misuse of NMS

Nicotine Mouth Spray



Dosage Form: 1 mg nicotine per spray solution

Route: Oral mucosal

Dose: 18 years and older: 1-2 sprays; max 4 sprays/ hour; max 64 sprays/ day

Indication: To reduce withdrawal symptoms including nicotine craving, associated with quitting smoking

Dosing Regimen



- **Step 1 (Weeks 1-6):** use 1 to 2 sprays whenever you would normally smoke a cigarette or have a craving to smoke
- **Step 2 (Weeks 7-9):** start reducing the number of sprays per day, by week 9 you should be using half the number of sprays per day that you used in Step 1
- **Step 3 (Weeks 10-12):** continue reducing the number of sprays per day, so that you are not using more than 4 sprays per day during week 12

Nicotine Mouth Spray



Source: Applicant Submission

Nicotine Mouth Spray



Source: Applicant Submission

Approved Treatment Options

Drug	Formulation	Dose	Route
Nicotine Polacrilex	Gum	2, 4 mg	Buccal
	Lozenge	2, 4 mg	
	Mini lozenge	2, 4 mg	
Nicotine	Patch	7, 14, 21 mg	Dermal
Nicotine	Inhalant	4 mg/ cartridge	Orally inhaled
	Nasal spray	0.5 mg/ spray	Intranasal
Bupropion	Tablet	150 mg	Oral
Varenicline	Tablet	0.5, 1 mg	Oral

OTC Drug Requirements

- Benefits outweigh risks
- Potential for misuse and abuse is low
- Consumers can self-diagnose the condition
- Product can be adequately labeled
- Health care professional is not needed for safe and effective use

Real-World Efficacy Study



- Provides evidence of efficacy and safety in OTC setting
- Demonstrate effectiveness with package labeling, self-help material
- No training and education on product use
- No additional behavioral support

NDA Submission

- Clinical Development Program
 - 2 Phase 3 safety and efficacy studies, 1 Phase 3 terminated study
 - 1 open-label pilot study
 - 4 clinical pharmacology studies
- Consumer Studies
 - Label comprehension study
 - Human factors study
- Postmarketing data

Meeting Objectives

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- Discuss potential for abuse and misuse of NMS



Nonprescription Drugs Advisory Committee
Meeting for Nicotine Mouth Spray 1 mg

Efficacy and Safety Data in Clinical Trials

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Division of Anesthesia, Analgesia,
And Addiction Products

Kate Meaker, MS
Statistical Reviewer
Division of Biometrics II

Outline

- Background
 - Over-the-counter nicotine replacement
 - Regulatory history of this application
- Product Description
- Indication, Dosage & Administration Instructions
- Efficacy
 - Phase 3 Controlled Studies
 - A6431111- “Study 11”
 - CO140121222102-SCCT, formerly NICTDP3038- “Study 38”
- Safety
- Conclusions

History of Over-the-Counter NRT

- 1984: Nicorette Gum 2 mg approved for prescription use as adjunctive therapy to behavioral treatment
- Early 1990s: Prescription approvals of Nicorette Gum 4 mg and four different transdermal products, all labeled as adjunctive treatment
 - “Minimal intervention” studies rare
- Over-the-Counter (OTC) switch requirements articulated by FDA review division
 - Develop and test “self-help” materials (in lieu of behavioral counseling)
 - Simulated OTC studies: all-comers, self-selection, purchase of product
 - Compare to “real-world” quit rate
 - Consistent findings of Continuous Abstinence Rate (CAR) Weeks 2-6 in range of 15%-20% on active treatment
- Direct-to-OTC approvals
 - Simulated OTC (low intervention, self-selection) placebo-controlled, double-blind study
 - PK-only programs referencing similar product

Regulatory History



- Pre-IND meeting with advice on development program in 2007
- A traditional, “prescription-like” randomized controlled trial was completed in Europe
- OTC trial was completed in the United States

NDA Submission

- Clinical Development Program- 9 studies
 - 2 Phase 3 safety and efficacy studies, 1 Phase 3 terminated study
 - 1 Open-label pilot study
 - 4 Clinical pharmacology studies
- Consumer Studies
 - Label comprehension study
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- Post marketing data



Nicotine Mouth Spray

Dosage Form: 1 mg nicotine per spray solution

Route: Oral mucosal

Dose: 18 years and older: 1-2 sprays; max 4 sprays/ hour; max 64 sprays/ day

Indication: To reduce withdrawal symptoms including nicotine craving, associated with quitting smoking

Source: Applicant Submission

Efficacy

Study 11 & Study 38

Phase 3 Studies

Study 11	Study 38
P3, R, DB, PC trial in 479 Smokers, NMS: Placebo 2:1	P3, R, DB, PC trial in 1198 Smokers, NMS: Placebo 1:1
6 weeks Tx, 6 weeks taper, 12 weeks occasional use, 30 day safety f/u, then 24 weeks no Tx, for a total of 52 weeks	12 weeks Tx, 14 weeks f/u
Last drug dispensed at week 20	Drug available for full 26 weeks
3 Centers in Europe	8 Centers in United States
Product Training & Smoking Cessation Counseling	No product training nor Smoking Cessation Counseling, OTC environment
Primary Endpoints: CA week 2-6, 24, and 52 verified by exhaled CO < 10 ppm	Primary Endpoints: CA week 2-6, verified by exhaled CO < 10 ppm at week 2, 4, and 6 visits

P3= Phase 3
 R= Randomized
 DB= Double-Blind
 PC= Placebo-Controlled
 NMS= Nicotine Mouth Spray
 Placebo= Placebo
 Tx= Treatment
 OTC= Over-the-counter
 CA= Continuous Abstinence
 CO= Carbon Monoxide
 PPM= parts per million

Source: Applicant
 Submission

Dosing Regimen and Instructions



- Weeks 1-6: 1-2 sprays every 30-60 minutes, maximum 4 sprays/hour, or 64 sprays/day
- Weeks 7-9: Reduce number of sprays/day, by week 9, use half the average number of sprays/day
- Weeks 10-12: Reduce number of sprays/day to no more than 4 sprays/day by week 12

Source: Applicant Submission

Demographics and Baseline Characteristics

Demographics	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Age (years) Mean (SD)	47 (10.9)	46 (11.3)	51 (11.7)	51 (11.7)
Gender				
Male	181 (57)	88 (55)	265 (44)	282 (47)
Female	137 (43)	73 (45)	332 (56)	319 (53)
Race				
White	313 (98)	161 (100)	345 (58)	373 (62)
People of Color	5 (2)		252 (42)	228 (38)

NMS= Nicotine Mouth Spray

SD= Standard Deviation



Background Characteristics	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Baseline # CPD				
Mean (SD)	23(8.8)	23(8.7)	18(8.5)	18(7.7)
Range	6-65	4-61	3-70	2-60
< 20 n(%)	92(29)	48(30)	297(50)	295(49)
≥ 20 n(%)	226(71)	113(70)	300(50)	306(51)
Baseline FTND				
Mean (SD)	5.3(2.3)	5.4(2.2)	5.2(2.0)	5.4(2.2)
TTFC				
≤ 30 min	233(73)	125(78)	510(86)	489(81)
> 30 min	85(27)	36(22)	86(14)	112(19)

NMS= Nicotine Mouth Spray

SD= Standard Deviation

CPD=Cigarettes Per Day

FTND=Fagerström Nicotine Dependence Score

TTFC= Time to First Cigarette

Source: FDA Statistical Review

Efficacy Results

Kate Meaker, MS
Statistical Reviewer
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Summary of Efficacy Results

Primary Endpoint:

Continuous Abstinence from Weeks 2 through 6

Both studies demonstrated statistically significant differences compared to placebo

The magnitude of the treatment effect was much smaller in the OTC setting study than in the traditional clinical study

Summary of Efficacy Results

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Responders, n (%)	83 (26%)	26 (16%)	30 (5%)	15 (2%)
Diff. (NMS – Placebo)	10%		3%	
95% Conf. Interval on Diff.	(2%, 17%)		(0%, 5%)	
P-value	0.014		0.022	

Traditional Clinical Study

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Responders, n (%)	83 (26%)	26 (16%)	30 (5%)	15 (2%)
Diff. (NMS – Placebo)	10%		3%	
95% Conf. Interval on Diff.	(2%, 17%)		(0%, 5%)	
P-value	0.014		0.022	

OTC Setting Study

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Responders, n (%)	83 (26%)	26 (16%)	30 (5%)	15 (2%)
Diff. (NMS – Placebo)	10%		3%	
95% Conf. Interval on Diff.	(2%, 17%)		(0%, 5%)	
P-value	0.014		0.022	

Disposition N (%)	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Discontinued Prior to Week 6	58 (18%)	45 (28%)	77 (13%)	85 (14%)
Discontinued After Week 6 but Prior to End of Treatment	73 (23%)	36 (22%)	105 (18%)	123 (20%)
Discontinued after End of Treatment	20 (6%)	5 (3%)	50 (8%)	41 (7%)
Completed Study	167 (53%)	75 (47%)	365 (61%)	352 (59%)

Study 11:

End of Tx:

Wk 24

End of Study:

Wk 52

Study 38:

End of Tx:

Wk 12

End of Study:

Wk 26

Efficacy Results by Age

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	Mean Age = 47		Mean Age = 51	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Age < 50				
Responders, n (%)	49/188 (26%)	15/94 (16%)	10/226 (4%)	6/230 (3%)
Diff. (NMS – Placebo)	10%		1%	
Age ≥ 50				
Responders, n (%)	34/130 (26%)	11/67 (16%)	20/371 (5%)	9/371 (2%)
Diff. (NMS – Placebo)	10%		3%	

Efficacy Results by Gender

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	Females = 44%		Females = 54%	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Females				
Responders, n (%)	25/137 (18%)	5/73 (7%)	15/332 (5%)	7/319 (2%)
Diff. (NMS – Placebo)	11%		3%	
Males				
Responders, n (%)	58/181 (32%)	21/88 (7%)	15/265 (6%)	8/282 (3%)
Diff. (NMS – Placebo)	7%		3%	

Efficacy Results by Race

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	White = 99%		White = 60%	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
White Responders, n (%) Diff. (NMS – Placebo)	82/313 (26%) 10%	26/161 (16%)	21/345 (6%) 3%	10/373 (3%)
People of Color Responders, n (%) Diff. (NMS – Placebo)	1/5 (20%) na	0/0	9/252 (4%) 2%	5/228 (2%)

Efficacy Results by Number Cigarettes Smoked / Day



Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	Baseline #cigs < 20 = 29%		Baseline #cigs < 20 = 49%	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Baseline #cigs < 20 Responders, n (%) Diff. (NMS – Placebo)	27/92 (29%) 10%	9/48 (19%)	15/297 (5%) 3%	7/295 (2%)
Baseline #cigs ≥ 20 Responders, n (%) Diff. (NMS – Placebo)	56/226 (25%) 10%	17/113 (15%)	15/300 (5%) 2%	8/306 (3%)

Efficacy Results by Fagerström Test for Nicotine Dependence



Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	Baseline FTND < 6 = 51%		Baseline FTND < 6 = 54%	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Baseline FTND < 6 Responders, n (%) Diff. (NMS – Placebo)	48/163 (29%) 11%	14/80 (18%)	16/318 (5%) 3%	6/329 (2%)
Baseline FTND ≥ 6 Responders, n (%) Diff. (NMS – Placebo)	35/155 (29%) 14%	12/81 (15%)	14/278 (5%) 2%	9/272 (3%)

Efficacy Results by Time to First Cigarette



Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	TTFC ≤ 30 mins = 75%		TTFC ≤ 30 mins = 83%	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Baseline TTFC ≤ 30 mins. Responders, n (%) Diff. (NMS – Placebo)	56/233 (24%) 10%	18/125 (14%)	25/510 (5%) 3%	11/489 (2%)
Baseline TTFC > 30 mins. Responders, n (%) Diff. (NMS – Placebo)	27/85 (32%) 10%	8/36 (22%)	5/86 (6%) 2%	4/112 (4%)

None of the patient characteristics we considered could account for the disparity in abstinence rates across the two studies.

Representations of Success Rates

$$\text{Odds Ratio} = \frac{\widehat{p}_{\text{TRT}} (1 - \widehat{p}_{\text{Placebo}})}{\widehat{p}_{\text{Placebo}} (1 - \widehat{p}_{\text{TRT}})}$$

$$\text{Difference in Success Rates} = \widehat{p}_{\text{TRT}} - \widehat{p}_{\text{Placebo}}$$

$$\text{Number Needed to Treat (NNT)} = \frac{1}{\text{Diff. in Success Rates}}$$

Number Needed To Treat

Continuous Abstinence Rate Weeks 2 through 6	Study 11		Study 38	
	NMS N=318	Placebo N=161	NMS N=597	Placebo N=601
Responders, n (%)	83 (26%)	26 (16%)	30 (5%)	15 (2%)
Diff. (NMS – Placebo)	10%		3%	
Number Needed to Treat	10		40	

NRT Reference: Commit Lozenge

Continuous Abstinence Rate Weeks 2 through 6	Self-Identified Low Dose		Self-Identified High Dose	
	Commit 2mg N=459	Placebo N=458	Commit 4mg N=450	Placebo N=451
Responders, n (%)	211 (46%)	136 (30%)	219 (49%)	94 (21%)
Diff. (NMS – Placebo)	16%		28%	
Number Needed to Treat	6.1		3.6	

Efficacy Conclusions

- The efficacy results demonstrated statistically significant differences
- The magnitude of the treatment effects is questionable with respect to clinical relevance, as demonstrated by the difference in success rates and the number needed to treat

Safety Results

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Safety Review Approach

- Nicotine's effects are fairly well-characterized
- Emphasis is on any formulation-specific findings that might be relevant in the risk-benefit assessment
- Local irritation was a particular concern
 - Reviewed by dental consultant from Division of Dermatology and Dental Products
 - Placebo spray contained capsaicin to mimic the taste of nicotine, so local irritation findings from both arms are relevant
- Persistent use is an issue of concern as a possible indicator of abuse potential

Safety Database



R= Randomized
 DB= Double-Blind
 PC= Placebo-Controlled
 OTC= Over-The-Counter
 OL= Open-Label
 AC= Active Comparator
 PK= Pharmacokinetic
 PD= Pharmacodynamic
 SD= Single Dose
 MD= Multi-Dose
 *Studies with active
 comparator, no placebo

Source: Applicant
 Submission

Study	Design	Duration	Treatment N	
			NMS	Placebo
Phase 3, Randomized Controlled Studies				
A6431111, “Study 11”	R,DB,PC	52 weeks (12 wks tx)	318	161
NICTDP3038, ”Study38”	R,DB,PC, “OTC”	26 weeks (up to 26 wks tx)	597	601
Other Efficacy Studies				
NICTDP2010	OL, R, fixed vs flex dosing	3 weeks	258	0
A6431112	R,DB, PC, early termination	4 weeks	13	242
Clinical Pharmacology*				
NICTDP1066	R, MD, AC, PK	5 visits	40	0
NICTDP2011	R, SD, AC, PD	3 visits	200	0
A6431094	R, SD, AC, PK	4 visits	31	0
A64331107	R, SD, AC, PK	6 visits	24	0
NICTDP1065	R, SD, AC, PK	5 visits	45	0

Serious Adverse Events

- Deaths
 - No deaths reported in Phase 1 and Phase 2 studies
 - Phase 3 Studies
 - Study 11:
 - 1 subject in active arm
 - Study 38:
 - 2 subjects in active arm
 - 4 studies in placebo arm
 - Study A6431112:
 - 1 subject in placebo arm
- No deaths attributable to study drug

Source: Applicant Submission

Non-Fatal Serious Adverse Events



- Phase 1 studies: 2 SAEs
- Phase 2 studies: 5 SAEs
- Phase 3 terminated study: 4 SAEs
- Pivotal Phase 3 studies: 19 Placebo subjects, 33 NMS subjects
- No SAEs were attributable to study drug

Discontinuations

- Study 11: 41 subjects withdrew due to AEs
 - 12 (7%) placebo, 3 subjects had > 1 AE, most common was dyspepsia 4 (2.5%)
 - 29 (9%) NMS, 3 subjects had > 1 AE, most common was nausea 10 (3.1%)
- Study 38: 40 subjects withdrew due to AEs
 - 16 (2.7%) placebo, most common was tooth abscess 3(0.5%)
 - 24 (4%) NMS, most common was hiccups 9(1.5%)

Common Adverse Events



- The most common treatment-emergent AEs in the active arm of both pivotal studies were hiccups, headaches, and local throat irritation
- Several common AEs in the active arm of both pivotal studies affected the gastrointestinal and nervous systems, which is typical in smoking cessation studies:
 - Nausea, vomiting, heartburn, and dizziness

Study 11

Top Ten Common Adverse Events $\geq 2\%$ of Active Arm

Preferred Term	NMS %	Placebo %
Hiccups	72	9
Headache	50	57
Throat Irritation	45	35
Nausea	41	32
Common Cold	34	39
Heartburn	36	17
Mouth Irritation	28	19
Dizziness	26	34
Constipation	24	19
Dry Mouth	19	17

All these terms were solicited in the e-diary, which may have increased reporting rate.

Findings of Visual Mouth Inspections were not included as AEs in the CRF

Study 38

Top Ten Common Adverse Events $\geq 2\%$ of Active Arm

Preferred Term	NMS %	Placebo %
Hiccups	42	8
Nausea	10	4
Headache	8	6
Nasopharyngitis	6	4
Upper Resp Inf	6	4
Hypertension	5	3
Dyspepsia	4	3
Cough	4	3
Oropharyngeal pain	4	3
Throat Irritation	4	2

Adverse Events of Interest: Local Irritation



- Nicotine is a known local irritant
- Placebo spray was also irritating
- Proposed max dose of NMS of 64 sprays, or 64 mg/day, which is more frequent than other oromucosal NRTs
- For **Study 11 Visual Mouth Inspection (VMI)** was performed at baseline, Weeks 2, 12, and 24 and not recorded as AEs
- In **Study 38** VMI was performed by dentists or qualified dental professionals at baseline and Week 6 (or end of study if subject withdrawal before Week 6) and the findings included in the AE and TEAE tabulations

Significant VMI findings

- Study 11: ≥ 1 new oral abnormalities or lesions were reported for 5.7% of subjects in the NMS group vs 4.3% in the placebo group
- Study 38
 - 2.5% (15 subjects) in the NMS group and 1.2% (7 subjects) in the placebo group who had no abnormal lesions at baseline developed abnormal lesions at 6 weeks
 - For subjects who had 1 or more abnormalities at Week 6, 17.6% in the NMS group and 9.8% in the placebo group had a new or worsened oral condition

Persistent Use: Study 38



- Study 38: Subjects were permitted to request study medication for the study duration (beyond labeled 12-week period)
 - For subjects who provided use data:
 - Week 13: 92% of NMS subjects were continuing use
 - Week 26: 78.8% of NMS subjects were continuing use
 - Overwhelmingly, these subjects were non-abstinent
 - This represents 18% of ITT population, which exceeds 26-week quit rate of 3.4% at 26 weeks
 - Among Week 26 quitters: 50% not using product at all.

Source: Sponsor's Study Report

Conclusions

- Study 11 provides evidence that under the right circumstances, NMS can be more effective than placebo in helping smokers to quit.
- The results of Study 38 suggest that the translation of the product into a stand-alone for over-the-counter use (drug plus labeling plus self-help material) was not successful.
 - The tested conditions (“OTC” use) and studied population (US Consumers) are those currently proposed for marketing in this application.
- NMS is associated with hiccups, local oromucosal irritation, including significant new abnormalities, in addition to the typical NRT AEs such as nausea, vomiting, dizziness, and headaches. Persistent use among non-quitters was more likely than successful quitting.



Nonprescription Drugs Advisory Committee
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Postmarketing Safety Data

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September 18, 2019

Outline

- Overview
- Pharmacovigilance Databases
 - Global Safety Database (GSD)
 - FDA Adverse Event Reporting System (FAERS)
 - World Health Organization (WHO) VigiBase
- Literature
- Conclusion

Database Limitations

- Spontaneous reporting
 - Adverse events (AEs) underreported
 - Data often incomplete
 - Reporting biases
 - Cause and effect difficult to establish

Serious Adverse Event

21 CFR 312.32(a)

- Death • Life-threatening • Hospitalization
- Disability or Permanent Damage
- Congenital Anomaly or Birth Defect
- Require Intervention to Prevent Permanent Impairment or Damage; Other Important Medical Events
 - Blood dyscrasias
 - Seizures
 - Allergic bronchospasm
 - Development of drug dependence or drug abuse

Definition Drug Abuse and Misuse

Drug abuse

Intentional, nontherapeutic use of a drug product or substance even once, to achieve a desired psychological or physiological effect

Examples: Additional doses to achieve euphoria; Administration via an unapproved route

Drug misuse

Intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse

Examples: Additional dose of pain medication to alleviate pain; Additional dose of weight loss medication to achieve greater or faster weight loss; Taking a sleeping pill for insomnia from a friend

Definition Drug Dependence

Drug Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Examples: Caffeine; Clonidine; Amphetamines

Psychological dependence is a state in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug.

Example: Opioids

Dependence

- MedDRA preferred term (PT)
 - Drug dependence
 - Nicotine dependence
 - Dependence
- Report content
- Narrative evaluation

Nicotine Mouth Spray

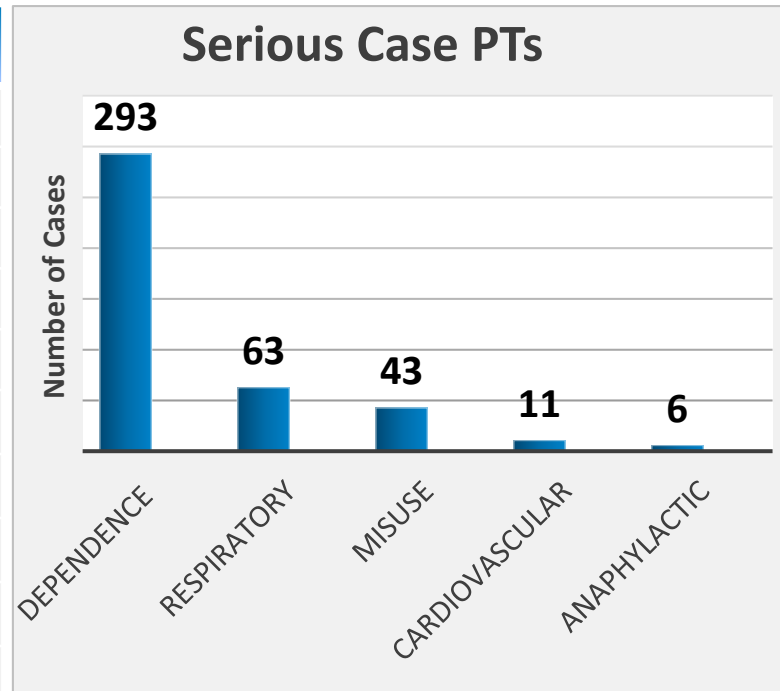
- Foreign approval 2010
- Behind-the-counter or front-of-counter (OTC) status in many countries
- Labeled for use down to 12 years of age in UK

GSD AEs for NMS 1 mg

- 7.5 years marketing (2011-2018)
- 4596 case reports; 9805 adverse events
 - 450 Serious cases; dependence most common SAE
 - 4146 Nonserious cases; hiccups and oral discomfort most common AE
 - No subgroup patterns identified

GSD Serious Case PTs Frequency ≥ 10

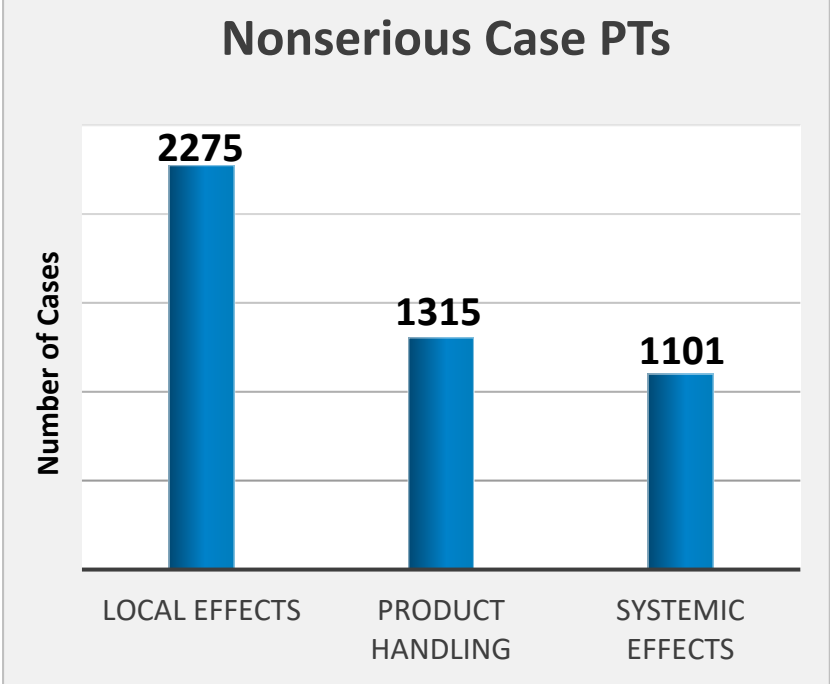
MedDRA PT	# Events/PT
Drug dependence	245
Incorrect drug administration duration	123
Nicotine dependence	31
Overdose	24
Dyspnea	21
Dependence	17
Product quality issue	15
Drug ineffective	12
Intentional product use issue; headache; asthma	11
Hiccups; pharyngeal edema; throat irritation; wrong technique in product usage process	10



450 cases reported 1143 AEs

GSD Nonserious Case PTs Frequency ≥ 100

MedDRA PT	# of Events
Hiccups	592
Oral discomfort	578
Throat irritation	499
Burning sensation	183
Oropharyngeal pain	118
Product quality issue	311
Drug administration error	159
Wrong technique in product usage process	127
Overdose	105



4146 cases reported 8662 AEs

GSD SAE and AE Demographics

Characteristic	Serious	Nonserious	Total
Source			
Spontaneous	448	4,135	4,583
Literature	2	11	13
Gender			
Female	208	1,943	2,151
Male	183	1,626	1,809
Not reported	59	577	636
Age Group (Years)			
0 to <2 (Infants)	0	1	1
2 to <13 (Child)	0	8	8
13 to <18 (Adolescent)	0	7	7
18 to <40	23	385	408
40 to <55	56	445	501
55 to <65	38	251	289
≥65 / Elderly	29	179	208
Adults total	150	1,379	1,529
Not reported	271	2,572	2,843

- Similar number of gender-based SAEs and AEs
- No reported pediatric/adolescent SAEs; few reported AEs

GSD Pediatric/Adolescent AEs

- 16 cases associated with NMS
- No serious cases
- AEs: burning sensation, dizziness, dyspnea, headache, malaise, nausea, pain, pallor, suffocation feeling, throat irritation, and vomiting.
 - 4 cases (0-10 years of age) 3 were accidental exposure, 1 report of wrong patient receiving medication
 - 6 cases (12-17 years of age) using NMS for the treatment for cessation of smoking or chewing tobacco
 - 5 cases from prescription nicotine spray for a 12-year-old girl shared with 20 classmates (11-13 year-olds) reported in UK newspaper

FDA FAERS and WHO Vigibase Search

- NMS case reports through April 2019
- Excluded case reports
 - Different form of NRT (e.g., gum, lozenge, patch, nasal spray)
 - No adverse event reported
 - Alternate etiology provided (e.g., concomitant medication, underlying disease state)
 - Report from a clinical trial (not postmarketing reports)
- Identified 96 FAERS and 180 WHO Vigibase cases

FAERS and WHO VigiBase Demographics



Characteristic		FAERS (N=96)	WHO VigiBase (N=180)
Age (years)	Mean	49	48
	Median	49	49
	Range	24-75	1-73
	No Report	47	99
Gender	Female	47	94
	Male	42	75
	No Report	7	11
Reporter	Consumer	48 (50%)	105 (58%)
	Healthcare Provider	48 (50%)	75 (42%)

FAERS and WHO Vigibase

Top 5 MedDRA PTs for NMS SAEs

FAERS SAEs		WHO Vigibase SAEs	
Nicotine Dependence	15 (15.6%)	Drug Dependence	56 (31%)
Dyspnea	10 (10.4%)	Incorrect Prod Admin Duration	30 (16.7%)
Intentional Product Use Issue	10 (10.4%)	Nicotine Dependence	19 (10.5%)
Overdose	10 (10.4%)	Intentional Product Use Issue	10 (5.5%)
Asthma	9 (9.4%)	Dyspnea	8 (4.4%)

Dependence/Misuse/Abuse Classification

- Case reports with one or more of the following:
 - The term(s) “drug abuse” or “drug misuse” or “drug dependence” is stated in the narrative
 - With or without clinical manifestations associated with drug abuse or misuse of, or dependence on, the drug of interest
- Clinical assessment by the reviewer of drug abuse, misuse, or dependence

FAERS and WHO Vigibase

Dependence/Misuse/Abuse			
FAERS		WHO Vigibase	
Dependence	24 (25%)	—	—
Misuse	18 (19%)	—	—
Abuse	3 (3%)	—	—

- FAERS narrative review resulted in classification of 26 cases with Dependence AND Misuse (15); Dependence ALONE (7); Misuse ALONE (1); Abuse ALONE (1); Dependence AND Misuse AND Abuse (2); all SAEs
- WHO Vigibase narratives not available for review

FAERS Oral NRT Dependence Search



Search Strategy:

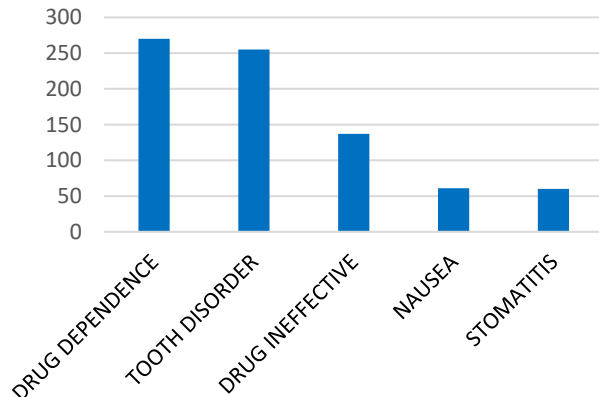
5-year timeframe beginning with product approval date

- Rx Gum: Nicorette 2 mg gum
Rx approval 1/13/1984 to 1/13/1989
- OTC Gum: Nicorette 2 & 4 mg gum
Rx-to-OTC switch 2/9/1996 to 2/9/2001
- OTC Lozenge: Nicorette 2 & 4 mg lozenge
OTC approval 10/31/2002 to 10/31/2007

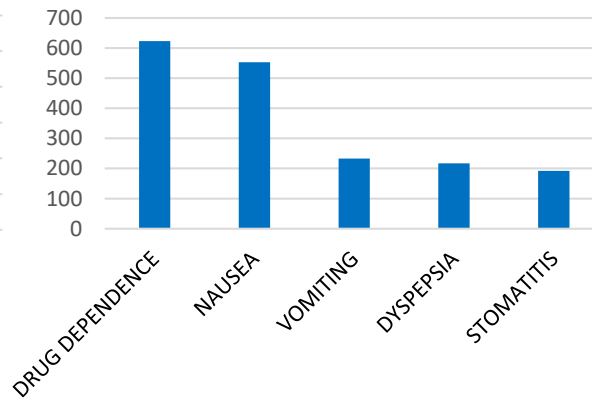
FAERS Oral NRT Dependence Search

“Drug dependence” (RX Gum, OTC Gum) or “Nicotine dependence” (OTC Lozenge) ranked amongst the top 3 PTs reported

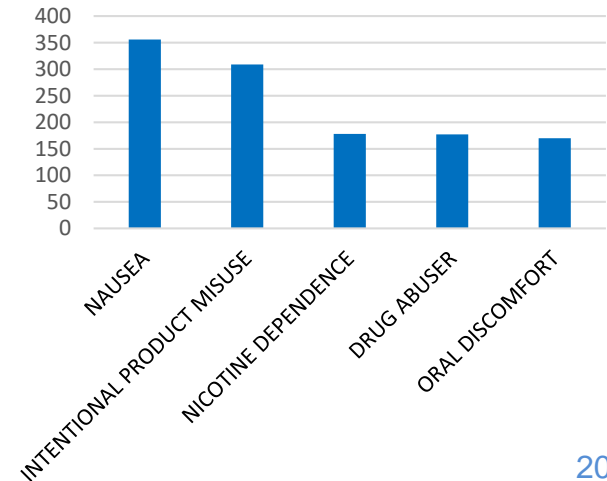
Rx Nicorette Gum 2 mg
Top 5 PTs Reported



OTC Nicorette Gum 2&4 mg
Top 5 PTs Reported



OTC Nicorette Lozenge 2&4 mg
Top 5 PTs Reported



Literature Search

- PubMed and Embase to July 2019 for NMS/NRTs
- 14 relevant publications
- 5 publications with 12 week NMS treatment
 - 3 of clinical trial data; 1 combination with patch treatment; 1 pilot study for preference, safety and efficacy

Literature Key Points

Author/Year	Study	Findings
Bolliger (2007)	OMS pilot study data	90 of 106 drug-related AEs due to spray with burning, nausea, and hiccup most frequent
Mills (2010)	Review of 92 NRT RCTs	Oral NRTs associated with throat soreness, mouth ulcers, hiccups, and coughing
Bailey (2012)	Review of 7 smoking cessation adolescent studies	Adolescents report similar AEs to adults
Tonnesen (2011, 2012)	NMS clinical trial data	87% reported AEs hiccups and throat irritation most common AEs
Cochrane (2018)	Review of NRTs	Reference to Tonnesen and Bailey AEs
Motooka (2018)	FAERS analysis of smoking cessation treatments 2004-2016	Dependence odds ratios for oral and buccal nicotine higher than transdermal route

Postmarketing Safety Summary

- GSD identification of dependence as the most frequently reported SAE is consistent with WHO Vigibase and FAERS search results
- Hiccups represent the most common nonserious event reported for NMS
- Publications specific to NMS identify common oral application AEs of hiccups and sore throat and a general similarity to AE profiles of other NRTs

Reviewer Conclusion

Postmarketing safety findings from pharmacovigilance database and literature searches show a safety profile of NMS similar to existing formulations of oral nicotine products marketed as NRTs.



Nonprescription Drugs Advisory Committee
Meeting for Nicotine Mouth Spray 1 mg

Label Comprehension Study

Barbara R. Cohen, MPA
Social Science Analyst
Division of Nonprescription Drug Products
U.S. Food and Drug Administration
September 18, 2019

Outline

- What is a Label Comprehension Study?
- Label Comprehension Study #181093
 - Objectives
 - Design and Conduct
 - Results
- Conclusions

What is a Label Comprehension Study (LCS)?



- For OTC products, the Drug Facts Label (DFL) contains the critical information that consumers need to know for safe and effective use

Proposed Drug Facts Label

- not for sale to those under 18 years of age
- proof of age required
- not for sale in vending machines or from any source where proof of age cannot be verified

TAMPER EVIDENT FEATURE: The spray container is protected in a clear plastic shell. Do not use if the sealed plastic shell is open or damaged.

Retain this package for complete product information.

**LIFT
HERE** 
**For Complete
Drug Facts Label**

Drug Facts

Active ingredient (in each spray)

Nicotine 1 mg Purpose
Stop smoking aid

Use

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have

- heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate
- high blood pressure not controlled with medication. Nicotine can increase blood pressure
- stomach ulcer or diabetes
- history of seizures

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

When using this product

- hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.

Stop use and ask a doctor if

- mouth problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as heartburn, nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Drug Facts (continued)

Keep out of reach of children and pets. Nicorette QuickMist Mouth Spray may have enough nicotine to make children and pets sick. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
- before using this product, read the enclosed User's Guide and Quick Start Guide for complete directions and other important information
- do not inhale when spraying
- for best results do not swallow for 2-3 seconds after spraying
- do not eat or drink for 15 minutes before using this spray or while using the spray
- rinse immediately with water if you spray in eyes as irritation will occur
- to increase your chance of success it is important to use the nicotine mouth spray according to the following 12-week schedule:

Step 1: Weeks 1-6

- begin using the nicotine mouth spray on your quit day
- in the first 6 weeks, use the nicotine mouth spray as directed in the table below; however, do not exceed the maximum dose

Use	Max per hour	Max per day
1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	4 sprays per hour	64 sprays per day

Step 2: Weeks 7-9

- start reducing the number of sprays per day
- by the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1

Step 3: Weeks 10-12

- continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12

• nicotine mouth spray is a medicine and must be used in a certain way to get the best results
• it is important to complete treatment. If you feel you need to use the Nicorette QuickMist Mouth Spray for a longer period to keep from smoking, talk to your health care provider.

Other information

- store at 20 - 25°C (68 - 77°F). Avoid excessive heat above 30°C (86°F).

Inactive ingredients

acesulfame potassium, dehydrated alcohol, glycerin, hydrochloric acid, menthol, mint flavor, poloxamer 407, propylene glycol, purified water, sodium bicarbonate, sucralose, tromethamine

Questions or comments?

1-800-XXX-XXXX

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What is a Label Comprehension Study (LCS)?



- LCS assesses the extent to which consumers understand the information on the DFL and then apply this information when making drug product use decisions in a hypothetical situation
- Conducted for most OTC NDAs
 - Foundational study in OTC consumer behavior studies program
- Addresses questions such as
 - Is the wording understandable to the average consumer?
 - Does it convey the key concepts required for the safe and effective use of the product?

LCS Best Practices

- Identify communication objectives (most important concepts that need to be understood by consumer)
- Construct a questionnaire that targets communication objectives in an unbiased way
- New statements that have not appeared previously in OTC labeling should be assessed
- Use test labeling as close as possible to final label

LCS Primary and Secondary Objectives



- Primary Objectives: Applicant identifies the most important label communication objectives from viewpoint of safety and efficacy
 - Target thresholds established a priori – based on clinical implications if consumers fail to adequately understand labeled items
 - Adequate comprehension is assessed by comparing the established threshold with the lower bound of the two sided 95% confidence interval
 - Typically LCS thresholds range from 90% (endpoints of most clinical concern) to 80% (important but not the most clinically concerning)
 - Thresholds are targets – they are not utilized in the same way as success thresholds for efficacy studies
- Secondary Objectives – label statements less critical to safe and appropriate use, yet clinically relevant
 - Typically not assessed against thresholds - point estimates reported

LCS Literacy Considerations

- FDA generally asks for 25-30% limited literacy representation in the study population
- Average reading level in the U.S. estimated at 8th grade
- DFL should be written at a 4th-8th grade reading level
- Limited literacy participants should be consumers with 4th-8th grade reading skills, as assessed by validated instruments such as the REALM (Rapid Estimate of Adult Literacy in Medicine)

LCS Conduct



- Generally recruitment is from an all-comers population, but targeted recruitment is appropriate at times
- Participants go to a research facility for a one on one interview; after consent forms and REALM are administered, they read the label at their own pace
- Then, the interviewer administers an “open book” test to assess whether they are aware of and can understand key elements of the label
- Typically third party scenario questions are utilized

LCS #181093 – Primary Objectives

- Comprehension of:
 - “Do not inhale when spraying”
 - “Rinse immediately with water if you spray in eyes as irritation will occur”
 - “Step 1: Maximum number of sprays per hour: 4”
 - “Step 1: Maximum number of sprays per day: 64”
 - Assessed at 80% target threshold

LCS #181093 – Secondary Objectives



- Comprehension of:
 - “Step 1: Use 1-2 sprays when you would normally smoke a cigarette or have a craving to smoke”
 - “Step 1: Use the second spray if your cravings are not reduced within a few minutes”
 - “For best results, do not swallow for 2-3 seconds after spraying”
 - “Step 2 – Start reducing the number of sprays per day”
 - “Step 2 – By the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1”



LCS #181093 – Secondary Objectives

- Comprehension of:
 - “Step 3 – Continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12.”
 - “To increase your chance of success it is important to use the nicotine mouth spray according to the following 12 week schedule.”
 - “When using this product, hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.”

LCS #181093 – Design and Conduct



- Conducted in September 2018 in ten geographically dispersed sites across the United States
- Total of 504 participants, males and females, ages 18+
- Total of 130 limited literacy participants, comprising 25.8% of the study population
- All participants either currently smokers or attempting to quit smoking
- An additional statement was added to the proposed DFL after the NDA was submitted; not assessed in LCS
 - Do not eat or drink for 15 minutes before using this spray or while using this spray

LCS #181093 Results: Primary Endpoints (80% threshold)



	n	%	CI	NL*	LL*
Do not inhale when spraying	462	91.7	(88.9, 93.9)	94.1	92.3
Rinse immediately with water if you spray in eyes as irritation will occur	392	77.8	(73.9, 81.3)	78.3	76.2
Step 1 – Maximum number of sprays per hour – 4 sprays per hour	463	91.9	(89.1, 94.1)	94.9	83.1
Step 1 – Maximum number of sprays per day – 64 sprays per day	451	89.5	(86.5, 92.0)	93.3	78.5

*NL- normal literacy, LL – limited literacy

LCS #181093 Results: Secondary Endpoints - General Use



Secondary Endpoint	n	%	NL*	LL*
For best results do not swallow for 2-3 seconds after spraying	472	93.7	94.1	92.3
Step 1 – Use the second spray if your cravings are not reduced within a few minutes	469	93.1	94.7	88.5
Hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.	409	81.2	83.2	75.4

*NL – normal literacy; LL – limited literacy

LCS #181093 Results: Secondary Endpoints - Key Dosing Steps



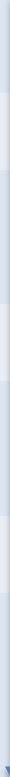


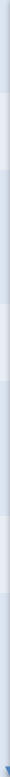


Secondary Endpoint	n	%	NL*	LL*
Step 1 – Use 1-2 sprays when you would normally smoke a cigarette or have a craving to smoke	444	88.1	89.8	83.1
Step 2 – By the end of week 9 you should be using half the average number of sprays per day that you used in Step 1	415	82.3	86.1	71.5
Step 3 – Continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12.	338	67.1	68.7	62.3

*NL – normal literacy; LL – limited literacy

LCS #181093 Results: Comprehension of Steps 1, 2, and 3



Step 1 (Two primary and one secondary endpoints)	Total	NL	LL
Maximum number of sprays per hour – 4 sprays per hour			
Maximum number of sprays per day – 64 sprays per day			
Use 1-2 sprays when you would normally smoke a cigarette or having a craving to smoke			
Step 2 (secondary)			
By the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1			
Step 3 (secondary)			
Continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12.			
Total Steps 1, 2, and 3 Combined	48.0%	52.4%	35.4%

Conclusions

- For most objectives, participants scored reasonably well on comprehension
 - However, additional statement on the DFL added after the LCS is an unknown factor
- The relatively low comprehension among all of “Rinse immediately with water if you spray into eyes as irritation will occur” may call for different placement or highlighting on the DFL
- Moreover, understanding the multiple dosing directions may be problematic for consumers:
 - Both NL and LL scored low on Step 3 and on all steps combined
 - DFL: *“To increase your chance of success, it is important to use the nicotine mouth spray according to the following 12-week schedule”*
 - DFL: *“Nicotine mouth spray is a medicine and must be used in a certain way to get the best results”*
 - Therefore, impact on potential efficacy unclear – we leave that to your discussion

Proposed Drug Facts Label

- not for sale to those under 18 years of age
- proof of age required
- not for sale in vending machines or from any source where proof of age cannot be verified

TAMPER EVIDENT FEATURE: The spray container is protected in a clear plastic shell. Do not use if the sealed plastic shell is open or damaged.

Retain this package for complete product information.

**LIFT
HERE** 
**For Complete
Drug Facts Label**

Drug Facts

Active ingredient (in each spray)

Nicotine 1 mg

Purpose

Stop smoking aid

Use

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Ask a doctor before use if you have

- heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate
- high blood pressure not controlled with medication. Nicotine can increase blood pressure
- stomach ulcer or diabetes
- history of seizures

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

When using this product

- hiccups or minor mouth and throat irritation may occur. Stop use and ask a doctor if these problems persist or worsen over the course of treatment.

Stop use and ask a doctor if

- mouth problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as heartburn, nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

Drug Facts (continued)

Keep out of reach of children and pets. Nicorette QuickMist Mouth Spray may have enough nicotine to make children and pets sick. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- If you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
- before using this product, read the enclosed User's Guide and Quick Start Guide for complete directions and other important information
- do not inhale when spraying
- for best results do not swallow for 2-3 seconds after spraying
- do not eat or drink for 15 minutes before using this spray or while using the spray
- rinse immediately with water if you spray in eyes as irritation will occur
- to increase your chance of success it is important to use the nicotine mouth spray according to the following 12-week schedule:

Step 1: Weeks 1-6

- begin using the nicotine mouth spray on your quit day
- in the first 6 weeks, use the nicotine mouth spray as directed in the table below; however, do not exceed the maximum dose

Use	Max per hour	Max per day
1-2 sprays when you would normally smoke a cigarette or have a craving to smoke (use the second spray if your cravings are not reduced within a few minutes)	4 sprays per hour	64 sprays per day

Step 2: Weeks 7-9

- start reducing the number of sprays per day
- by the end of week 9 you should be using HALF the average number of sprays per day that you used in Step 1

Step 3: Weeks 10-12

- continue reducing the number of sprays per day so that you are not using more than 4 sprays per day during week 12

- nicotine mouth spray is a medicine and must be used in a certain way to get the best results
- it is important to complete treatment. If you feel you need to use the Nicorette QuickMist Mouth Spray for a longer period to keep from smoking, talk to your health care provider.

Other information

- store at 20 - 25°C (68 - 77°F). Avoid excessive heat above 30°C (86°F).

Inactive ingredients

acesulfame potassium, dehydrated alcohol, glycerin, hydrochloric acid, menthol, mint flavor, poloxamer 407, propylene glycol, purified water, sodium bicarbonate, sucralose, tromethamine

Questions or comments?

1-800-XXX-XXXX

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Nonprescription Drugs Advisory Committee Meeting for Nicotine Mouth Spray 1 mg

FDA Charge to the Committee

Theresa M. Michele, MD

Director

Division of Nonprescription Drug Products

Center for Drug Evaluation and Research

September 18, 2019

Meeting Objectives

- Discuss efficacy and safety of over-the-counter (OTC) nicotine mouth spray (NMS) for smoking cessation
- Discuss potential for abuse and misuse of NMS

Nonprescription Drugs



Nonprescription drug products generally have these characteristics:

- Can be adequately labeled such that
 - The consumer can self-diagnose, self-treat, and self-manage the condition being treated
 - No health practitioner is needed for the safe and effective use of the product
- Drug has low potential for misuse and abuse
- Safety margin is such that the benefits of over-the-counter (OTC) availability outweigh the risks

Approval of an Application



- 21 CFR 314.105 (c)

“FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling”

Efficacy Standard



- 21 CFR 314.125 Refusal to Approve an Application

(b) (5) “... substantial evidence consisting of adequate and well-controlled investigations ... that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

Safety Standard



- 21 CFR 314.125 Refusal to Approve an Application

(b) (2) "... do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b) (3) "The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b) (4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Question 1: Discussion

Discuss the efficacy of nicotine mouth spray (1mg per spray) as an over-the-counter (OTC) smoking cessation aid. Consider the differences between the efficacy data from studies A6431111 and NICTDP3038.

Question 2: Discussion

Discuss the results of the label comprehension study and their implications for efficacy in the OTC consumer setting.

Question 3: Vote

Do the data provide substantial evidence of efficacy of nicotine mouth spray (1 mg per spray) as a smoking cessation aid in the OTC setting?

- a. If no, what further data should be obtained?

Question 4: Discussion

Discuss the safety of nicotine mouth spray (1 mg per spray) as a smoking cessation aid in the OTC setting.

Question 5: Discussion

Discuss the potential for abuse of nicotine mouth spray (1 mg per spray) by the adult and pediatric populations in the OTC setting. Consider its pharmacokinetic profile and other characteristics that are different from currently marketed OTC nicotine replacement therapy products.

Question 6: Vote

Do the data provide substantial evidence of safety of OTC use of nicotine mouth spray (1 mg per spray)?

- a. If no, what further data should be obtained?

Question 7: Vote

Is the benefit-risk profile of nicotine mouth spray (1 mg per spray) supportive of OTC use as a smoking cessation aid?

- a. If yes, do you have additional comments or recommendations for labeling?
- b. If no, what further data should be obtained?





Back-up Slide Shown



Primary Endpoint	Opened DFL unprompted (N=348)		Asked permission to open the DFL (N=32)		Did not open DFL until prompted (N=124)	
	n	%	n	%	n	%
Do not inhale when spraying	326	93.7	31	96.9	105	84.7
Rinse immediately with water if you spray in eyes as irritation will occur	269	77.3	29	90.6	94	75.8
Step 1 – Maximum number of sprays per hour – 4 sprays per hour	327	94.0	29	90.6	107	86.3
Step 1 – Maximum number of sprays per day – 64 sprays per day	324	93.1	31	96.9	96	77.4